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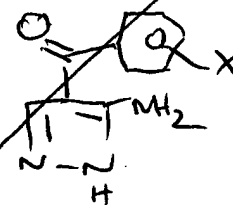
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54 (3-Amino-1H-pyrazol-4-yl)(aryl)methanones.

57 (3-Amino-1H-pyrazol-4-yl) (aryl)methanones which are
 new compounds having utility as anxiolytic agents or inter-
 mediates for the preparation of aryl and heteroaryl-[7-(aryl
 and heteroaryl)pyrazolo[1,5-a]pyrimidin-3-yl] methanones
 which are therapeutic agents described in copending applica-
 tion Ser. No. 506,966, filed June 23, 1983.

see Exs 84 →
 need to exclude



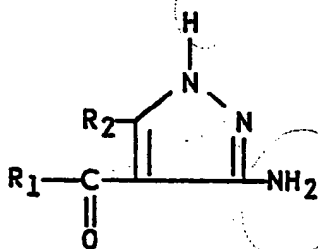
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TITLE: (3-AMINO-1H-PYRAZOL-4-YL) (ARYL)METHANONES

SUMMARY OF THE INVENTION

This invention relates to new organic compounds which may be represented by the following structural formula:

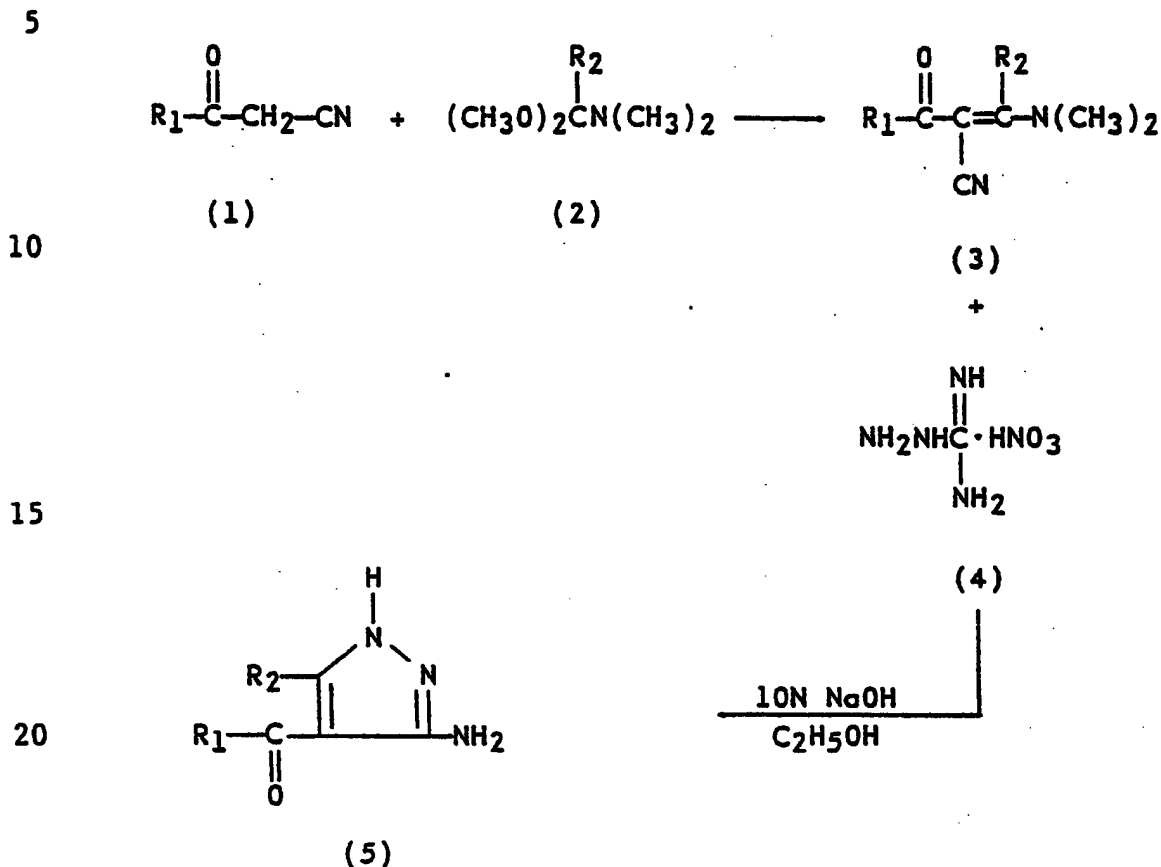


wherein R_1 is selected from the group consisting of phenyl substituted by one or two of the group selected from halogen, alkyl(C_1-C_3) and alkoxy(C_1-C_3); phenyl substituted by one of the group consisting of dialkylamino(C_1-C_3), methylenedioxy, alkylthio(C_1-C_3), alkylsulfonyl(C_1-C_3), substituted arylsulfonyl, amino, alkanoyl(C_1-C_3) amino, substituted aroylamino, trifluoromethyl and phenyl; pyridinyl; pyridinyl substituted by one or two of the group selected from halogen, alkyl(C_1-C_3) and alkoxy(C_1-C_3); thienyl; thienyl substituted by one or two of the group selected from halogen, alkyl(C_1-C_3) and alkoxy(C_1-C_3); furanyl; naphthalenyl; and pyrazinyl; and R_2 is selected from the group consisting of hydrogen and alkyl(C_1-C_3).

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DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention may be readily prepared as set forth in the following reaction scheme:



25 In accordance with the above reaction scheme an appropriately substituted acetonitrile (1), where R₁ is as described above is reacted with a dimethylamide dimethyl-acetal (2) where R₂ is as described above. The resulting exothermic reaction produces a crystalline solid which is recovered by evaporation and dissolved in methylene chloride. This solution is passed through hydrous magnesium silicate and hexane is added to the refluxing eluate, giving the [(α-dimethylamino)methylene]-β-oxoarylpropan-nitrile (3) which is then reacted with aminoguanidine nitrate (4) in the presence of 10N sodium hydroxide and a

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lower alkanol at reflux for several hours then evaporated to dryness and crystallized from water, ethanol or other suitable solvent, giving (5). The aminoguanidine nitrate may be replaced by other salts of aminoguanidine, such as the hydrochloride, sulfate, and the like. Alternatively, the aminoguanidine salt-sodium hydroxide combination may be replaced by an equivalent of aminoguanidine bicarbonate or thiosemicarbazide, both reagents resulting in the formation of (5).

The (3-amino-1H-pyrazol-4-yl)(aryl)methanones find utility as intermediates in the preparation of therapeutic aryl and heteroaryl[7-(aryl and heteroaryl)pyrazolo-[1,5-a]pyrimidin-3-yl]methanones which are the subject of the simultaneously filed European Patent Application by the applicant with the title "Aryl and heteroaryl[7-(aryl and heteroaryl)pyrazolo-[1,5-a]pyrimidin-3-yl]-methanones" based on US-Serial No. 506 966 of June 23, 1983.

Such final products are useful as anxiolytic or anti-epileptic agents as well as sedative-hypnotic and skeletal muscle relaxant agents. The novel compounds of the instant invention additionally have utility as anxiolytic agents.

The following non-limiting examples illustrate the preparation of the compounds of the present invention.

Example 1

α -[(Dimethylamino)methylene]- β -oxo-2-furanepropanenitrile

A 50 ml portion of dimethylformamide dimethyl-acetal was added to 25 g of solid β -oxo-2-furanepropanenitrile. This exothermic reaction produced yellow crystals. After one hour the volatiles were removed under reduced pressure and the residue was dissolved in methylene chloride. This solution was passed through a short pad of hydrous magnesium silicate. The eluate was refluxed with the gradual addition of hexane to the point of turbidity. Cooling and filtration gave 35.2 g of the desired compound, mp 117-125°C.

Example 2 α -[(Dimethylamino)methylene]- β -oxo-benzene-
propanenitrile

5 A 100 g portion of β -oxo-benzenepropanenitrile
was placed in a 500 ml round-bottom flask and 110 ml of
dimethylformamide dimethylacetal was added in one portion.
The reaction mixture became warm and a homogeneous dark
yellow solution resulted, which then solidified. After
cooling to room temperature, hexane was added giving crystals
10 which were recovered by filtration. This material
(143.6 g, mp 102-105°C) is suitable for the subsequent
reaction without further purification.

An analytical sample of this compound was
obtained by dissolution in methylene chloride followed by
15 passage through a short column of hydrous magnesium silicate,
concentration of the eluate with the gradual addition of hexane
until crystallization occurred, cooling and collection by filtration,
mp 111-113°C.

Following the general procedures of Examples 1
20 or 2, the following compounds of Examples 3-31, shown in
Table I were prepared.

TABLE I

Example	Acetonitrile	Compound	MPOC
3	β -oxo-4-fluorobenzenepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-fluorobenzenepropanenitrile	142-145
4	β -oxo-(3-trifluoromethyl)benzenepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-(trifluoromethyl)benzenepropanenitrile	93-96
5	β -oxo-4-pyridinepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-pyridinepropanenitrile	127-128
6	β -oxo-2-thiophenepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-thiophenepropanenitrile	136-140
7	β -oxo-4-methylbenzenepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-methylbenzenepropanenitrile	132-135
8	β -oxo-2-pyridinepropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-pyridinepropanenitrile	88-90
9	β -oxo-3-fluorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-fluorophenylpropanenitrile	63-68
10	β -oxo-2-chlorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-chlorophenylpropanenitrile	152-154

TABLE I (continued)

Example	Acetonitrile	Compound	MPOC
11	β -oxo-3-furanylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-furanylpropanenitrile	98-103
12	β -oxo-3,4,5-trimethoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3,4,5-trimethoxyphenylpropanenitrile	138-140
13	β -oxo-3,4-dimethoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3,4-dimethoxyphenylpropanenitrile	glassy solid
14	β -oxo-3-methylphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-methylphenylpropanenitrile	74-80
15	β -oxo-3,5-dimethoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3,5-dimethoxyphenylpropanenitrile	125-127
16	β -oxo-4-chlorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-chlorophenylpropanenitrile	118-121
17	β -oxo-4-methoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-methoxyphenylpropanenitrile	128-130
18	β -oxo-2-fluorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-fluorophenylpropanenitrile	62-74

TABLE I (continued)

Ex.	Acetonitrile	Compound	MP°C
19	β -oxo-3-methoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-methoxyphenylpropanenitrile	Syrup
20	β -oxo-[4-(trifluoromethyl)phenyl]propanenitrile	α -[(dimethylamino)methylene]- β -oxo-[4-(trifluoromethyl)phenyl]propanenitrile	122-123
21	β -oxo-3-chlorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-3-chlorophenylpropanenitrile	Syrup
22	β -oxo-2,5-dichlorophenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2,5-dichlorophenylpropanenitrile	140-143
23	β -oxo-2-methylphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-methylphenylpropanenitrile	82-84
24	β -oxo-[4-(dimethylamino)phenyl]propanenitrile	α -[(dimethylamino)methylene]- β -oxo-[4-(dimethylamino)phenyl]propanenitrile	208-210
25	β -oxo-2-methoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-methoxyphenylpropanenitrile	105-115
26	β -oxo-[3,4-(methylenedioxy)phenyl]propanenitrile	α -[(dimethylamino)methylene]- β -oxo-[3,4-(methylenedioxy)phenyl]propanenitrile	118-124
27	β -oxo-4-ethoxyphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-ethoxyphenylpropanenitrile	110-115
28	β -oxo-4-ethylphenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-4-ethylphenylpropanenitrile	48-54

TABLE I (continued)

Ex.	Acetonitrile	Compound	MP°C
29	β -oxo-2-naphthalenylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-naphthalenylpropanenitrile	115-118
30	β -oxo-5-methyl-2-thienylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-5-methyl-2-thienylpropanenitrile	152-153
31	β -oxo-2-thienylpropanenitrile	α -[(dimethylamino)methylene]- β -oxo-2-thienylpropanenitrile	118-120

Example 32 α -[(1-Dimethylamino)ethylidene]- β -oxo-phenylpropanenitrile

5 A solution of 14.5 grams of benzoylacetonitrile
 in 100 ml of chloroform was cooled to -10°C and stirred as
 a solution of 13.3 g of N,N-dimethylacetamide dimethylace-
 tal in 20 ml of chloroform was added dropwise during 15
 minutes. The reaction temperature was not allowed to exceed
 -5°C . Stirring was continued at -5° to -10°C for two hours
 10 after addition ended. The resultant reaction mixture was
 dissolved in 150 ml of benzene and the solution passed
 through a layer of hydrous magnesium silicate. Evaporation
 of the filtrate in air left a yellow residue which was puri-
 fied by recrystallization from a mixture of benzene and low
 15 boiling petroleum ether; yield, 5.8 g, mp 105° - 106°C .

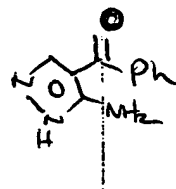
Example 33(3-Amino-1H-pyrazol-4-yl) (2-furanyl)methanone

A reaction mixture comprising 19.0 g of α -[(di-
 methylamino)methylene]- β -oxo-2-furanepropanenitrile,
 20 16.1 g of aminoguanidine nitrate, 250 ml of ethanol and
 11.0 ml of 10N sodium hydroxide was refluxed for 6 hours
 and then evaporated to dryness. Water was added to the
 crude residue and the precipitated solid was collected,
 giving 17.0 g of the desired product, mp 153 - 155°C .

Example 34(3-Amino-1H-pyrazol-4-yl) phenylmethanone

A reaction mixture comprising 73.36 g of α -[(di-
 methylamino)methylene]- β -oxo-2-benzenepropanenitrile,
 30 63.45 g of aminoguanidine nitrate, 500 ml of ethanol and
 36.6 ml of 10N sodium hydroxide was refluxed for 10 hours
 and then cooled. The resulting precipitate was collected
 and washed with water, giving 17.1 g of the desired pro-
 duct, mp 177 - 179°C .

35 When the aminoguanidine nitrate-10N sodium
 hydroxide combination was replaced by an equivalent of
 aminoguanidine bicarbonate, the identical product was
 obtained as shown by its melting point, elemental analysis



and infrared and nuclear magnetic resonance absorption spectra. A similar result was obtained when an equivalent of thiosemicarbazide replaced the aminoguanidine nitrate-10N sodium hydroxide combination.

5 Following the general procedures of Examples 33 and 34, employing the compounds of Examples 1-32 and the appropriate guanidine derivatives, the products of Examples 35-64, given in Table II, were prepared.

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TABLE II

Example	Starting Material of Example	Product	MPOC
35	3	(3-amino-1H-pyrazol-4-yl) (4-fluorophenyl)methanone	172-175
36	4	(3-amino-1H-pyrazol-4-yl) (3-(trifluoromethyl)phenyl)methanone	134-136
37	5	(3-amino-1H-pyrazol-4-yl) (4-pyridinyl)methanone	275-277
38	6	(3-amino-1H-pyrazol-4-yl) (2-thienyl)methanone	144-145
39	32	(3-amino-5-methyl-1H-pyrazol-4-yl) phenylmethanone	179-180
40	7	(3-amino-1H-pyrazol-4-yl) (4-methylphenyl)methanone	177-179
41	8	(3-amino-1H-pyrazol-4-yl) (2-pyridinyl)methanone	118-120
42	9	(3-amino-1H-pyrazol-4-yl) (3-fluorophenyl)methanone	188-189

TABLE II (continued)

Example	Starting Material Of Example	Product	MPOC
43	10	(3-amino-1H-pyrazol-4-yl)(2-chlorophenyl)methanone	glassy solid
44	11	(3-amino-1H-pyrazol-4-yl)(3-furanyl)methanone	211-215
45	12	(3-amino-1H-pyrazol-4-yl)(3,4,5-trimethoxyphenyl)methanone	199-201
46	13	(3-amino-1H-pyrazol-4-yl)(3,4-dimethoxyphenyl)methanone	108-109
47	14	(3-amino-1H-pyrazol-4-yl)(3-methylphenyl)methanone	137-139
48	15	(3-amino-1H-pyrazol-4-yl)(3,5-dimethoxyphenyl)methanone	91-92
49	16	(3-amino-1H-pyrazol-4-yl)(4-chlorophenyl)methanone	235-237
50	17	(3-amino-1H-pyrazol-4-yl)(4-methoxyphenyl)methanone	172-174
51	18	(3-amino-1H-pyrazol-4-yl)(2-fluorophenyl)methanone	glassy solid

TABLE II (continued)

Ex.	Starting Material of Example	Product	MP°C
52	19	(3-amino-1H-pyrazol-4-yl)-(3-methoxyphenyl)methanone	96-98
53	20	(3-amino-1H-pyrazol-4-yl)-[4-(trifluoromethyl)phenyl]methanone	172-174
54	21	(3-amino-1H-pyrazol-4-yl)-(3-chlorophenyl)methanone	229-230
55	22	(3-amino-1H-pyrazol-4-yl)-(2,5-dichlorophenyl)methanone	Syrup
56	23	(3-amino-1H-pyrazol-4-yl)-(2-methylphenyl)methanone	Glass
57	24	(3-amino-1H-pyrazol-4-yl)-[4-(dimethylamino)phenyl]methanone	240-243
58	25	(3-amino-1H-pyrazol-4-yl)-(2-methoxyphenyl)methanone	Glass
59	26	(3-amino-1H-pyrazol-4-yl)-[3,4-(methylenedioxy)phenyl]methanone	228-230
60	27	(3-amino-1H-pyrazol-4-yl)-(4-ethoxyphenyl)methanone	155-156
61	28	(3-amino-1H-pyrazol-4-yl)-(4-ethylphenyl)methanone	108-109

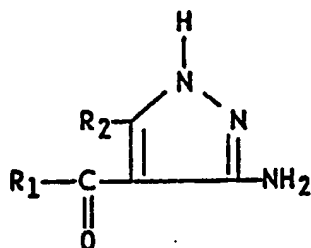
TABLE II (continued)

Ex.	Starting Material of Example	Product	MP°C
62	29	(3-amino-1H-pyrazol-4-yl)- (2-naphthalenyl)methanone	215-217
63	30	(3-amino-1H-pyrazol-4-yl)- (5-methyl-2-thienyl)metha- none	165-166
64	31	(3-amino-1H-pyrazol-4-yl)- (2-thienyl)methanone	181-183

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We claim:

1. A compound of the formula:

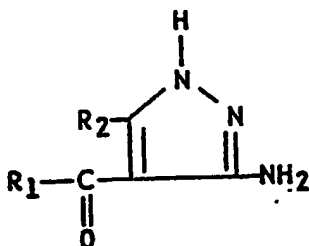


wherein R_1 is phenyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); phenyl substituted by one of dialkylamino(C_1-C_3), methylenedioxy, alkylthio(C_1-C_3), alkylsulfonyl(C_1-C_3), substituted arylsulfonyl, amino, alkanoyl(C_1-C_3) amino, substituted aroylamino, trifluoromethyl or phenyl; pyridinyl; pyridinyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); thienyl; thienyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); furanyl; naphthalenyl; or pyrazinyl; and R_2 is hydrogen or alkyl(C_1-C_3).

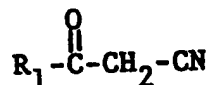
2. The compound according to Claim 1, (3-amino-1H-pyrazol-4-yl)(2-furanyl)methanone; (3-amino-1H-pyrazol-4-yl)(4-chlorophenyl)methanone; (3-amino-1H-pyrazol-4-yl)(4-fluorophenyl)methanone; (3-amino-1H-pyrazol-4-yl)-(4-methoxyphenyl)methanone; (3-amino-1H-pyrazol-4-yl)[3-(trifluoromethyl)phenyl]methanone; (3-amino-1H-pyrazol-4-yl)(4-pyridinyl)methanone; (3-amino-1H-pyrazol-4-yl)-(2-thienyl)methanone; (3-amino-5-methyl-1H-pyrazol-4-yl)-phenylmethanone; (3-amino-1H-pyrazol-4-yl)(4-methylphenyl)methanone; (3-amino-1H-pyrazol-4-yl)(2-pyridinyl)-methanone; (3-amino-1H-pyrazol-4-yl)(3-fluorophenyl)methanone; (3-amino-1H-pyrazol-4-yl)(3-furanyl)methanone; (3-amino-1H-pyrazol-4-yl)(3,4,5-trimethoxyphenyl)methanone; (3-amino-1H-pyrazol-4-yl)(3,4-dimethoxyphenyl)methanone; (3-amino-1H-pyrazol-4-yl)(3-methylphenyl)methanone; (3-amino-1H-pyrazol-4-yl)(3,5-dimethoxyphenyl)methanone; or (3-amino-1H-pyrazol-4-yl)(2-fluorophenyl)methanone.

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3. A process of preparing a compound of the formula:



wherein R_1 is phenyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); phenyl substituted by one of dialkylamino(C_1-C_3), methylenedioxy, alkylthio(C_1-C_3), alkylsulfonyl(C_1-C_3), substituted arylsulfonyl, amino, alkanoyl(C_1-C_3)amino, substituted aroylamino, trifluoromethyl or phenyl; pyridinyl; pyridinyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); thienyl; thienyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); furanyl; naphthalenyl; or pyrazinyl; and R_2 is hydrogen or alkyl(C_1-C_3) which comprises reacting an appropriately substituted acetonitrile of the formula



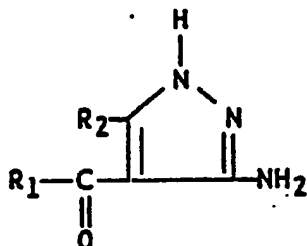
(where R_1 is as described above) with an N,N-dimethylamide dimethylacetal producing, after an exothermic reaction, a crystalline solid, recovering said crystalline solid, dissolving in methylene chloride, passing through hydrous magnesium silicate, adding hexane to the refluxing eluate, precipitating an $[(\alpha\text{-dimethylamino})\text{methylene}]$ -

β -oxoarylpropanenitrile of the formula $R_1-\overset{\overset{O}{\parallel}}{C}-\overset{\overset{R_2}{\mid}}{C}=\overset{\underset{\underset{CN}{\mid}}{C}}{C}-N(CH_3)_2$,

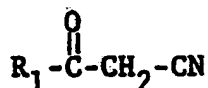
reacting with aminoguanidine salt in a lower alkanol solution of 10N sodium hydroxide at reflux for 6-10 hours, giving the desired product.

CLAIM FOR AUSTRIA

1. A process of preparing a compound of the formula:



wherein R_1 is phenyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); phenyl substituted by one of dialkylamino(C_1-C_3), methylenedioxy, alkylthio(C_1-C_3), alkylsulfonyl(C_1-C_3), substituted arylsulfonyl, amino, alkanoyl(C_1-C_3) amino, substituted aroylamino, trifluoromethyl or phenyl; pyridinyl; pyridinyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); thienyl; thienyl substituted by one or two of halogen, alkyl(C_1-C_3) or alkoxy(C_1-C_3); furanyl; naphthalenyl; or pyrazinyl; and R_2 is hydrogen or alkyl(C_1-C_3) which comprises reacting an appropriately substituted acetonitrile of the formula



(where R_1 is as described above) with an N,N-dimethylamide dimethylacetal producing, after an exothermic reaction, a crystalline solid, recovering said crystalline solid, dissolving in methylene chloride, passing through hydrous magnesium silicate, adding hexane to the refluxing eluate, precipitating an [(α -dimethylamino)methylene]-

- β -oxoarylpropanenitrile of the formula $R_1-\overset{\overset{O}{\parallel}}{C}-\underset{\underset{CN}{|}}{C}=\overset{\overset{R_2}{|}}{C}-N(CH_3)_2$,

reacting with aminoguanidine salt in a lower alkanol solution of 10N sodium hydroxide at reflux for 6-10 hours, giving the desired product.